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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,731	12/15/2003	Eberhard Weihe	029310.52995US	6798

23911 7590 03/09/2006

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EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,731	WEIHE ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-6, an d13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 12/14/05 has been made of record. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Election/Restriction

2. Applicant traverses the requirement for a restriction to a single polypeptide sequence made in the Requirement for election/restriction of 3/17/05 on the grounds that the sequences are similar and have the same function. The argument has been considered and not found to be persuasive for the reasons set forth in the requirement for restriction of 3/17/05 and in the office action of 6/14/05. In addition, in the action of 6/14/05, the examiner also invited Applicant to indicate positively that the different sequences were obvious over one another. Applicant is silent as to whether the different amino acid sequences are obvious over one anther in the subsequent amendment of 12/14/05. While the polypeptides are purported to transport glutamate, applicant has not defined the common structural elements related to that activity. Merely having sequence homology is not equivalent to identifying the structural elements essential for the function of the polypeptides. Therefore the requirement for restriction is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Objections/Rejections: Withdrawn

Claim Rejections - 35 USC § 112

3. Rejection of claims 9 under 35 USC § 112, 2nd paragraph, is withdrawn due to applicant's amendment. Applicant has amended to take out 'native' in 'native mammalian cell.'

Objections/Rejections: Maintained/New Grounds

Claim Rejections - 35 USC § 112

4. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC § 112, 1st paragraph, enablement is maintained for the reasons made of record in the office action dated 6/14/05 and the reasons below. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the specification contains numerous tests, which were performed in order to identify certain proteins as relevant to pain. The examiner notes that beginning at section 0086, the specification discloses measuring changes in gene expression related to the injection of Freud's adjuvant or collagen as an animal model of pain. However, there is ***no nexus*** between a change in expression between any one or more mRNAs or proteins, together as an ensemble or singularly expressed, and the pain in the animal. A change in expression of one protein among a large (undefined) number of proteins in an animal model of pain does not indicate that expression of that protein is linked to pain. Enhanced expression of BNPI (also called Vglut1) may have nothing at all to do with pain. Enhanced expression of BNPI in an

animal model of pain is merely an invitation to do additional research. One would have to further experiment to determine if expression of BNPI is really linked to pain in any way. Additionally, further experimentation would also be required to determine if a compound should inhibit, activate, or otherwise modulate BNPI. In short, injection of Freund's adjuvant or collagen causes elevated expression of Vglut1 and induction of pain. That does not mean elevated Vglut1 causes pain.

5. Neither prior nor post-filing date art supports a role of vglut1 in mediating pain. For instance, analysis of expression by microarray of proteins with a greater than two-fold change in an animal model of pain did not find that vglut1 (BNPI) was elevated (Sun et al 2002). Sun et al identify more than 50 proteins that show greater than two-fold expression in an animal model of pain (see Table I, page 3). However, Vglut1 is not among them. Further, Sun et al are silent as to whether any of the proteins identified by their method are necessarily involved in pain. Sun et al explain that the study is merely a starting point for determining if one or more of the genes actually represent appropriate therapeutic targets by having a role in pain modulation, saying "The aim of this study was to find genes that are enriched in the dorsal spinal cord ***that can potentially play important roles*** in pain transmission, pain modulation, and pathophysiological conditions [page 7, right col; emphasis added]." Thus, the art does not recognize that mere upregulation in these circumstances is predictive of causality.

Applicant argues that abstracts contained in appendix A of the Remarks indicate a method of using Vglut1 to identify compounds that modulate pain is enabled. Importantly, none of the abstract or titles link Vglut1 to pain. Additionally, several of the

abstracts indicate Vglut1 activity or expression changes *not related* to pain. For instance, Moutsimilli et al (and Tordera et al) of appendix A show that Vglut1 is enhanced *in the brain with antidepressant activity*. Thus, applicant has provided references that not only don't support 'a method to detect a pain-regulating compound,' but further *teach away* from a specific relationship between Vglut1 and pain.

Applicant argues on page 8 of Remarks that "There is nothing in the record to suggest any reason why the method would not work as claimed." In contrast to applicant's assertion, the entire prior rejection of 6/14/05 under 35 USC 112, 1st enablement, pages 3-5, and the above arguments all describe why the method will not detect compounds that regulate pain, as well as various other aspects of the claims that are not enable.

Applicant states on page 9 of Remarks, "it is important to note that the method is directed to detecting a pain-regulating substance, not measuring the degree to which a substance may regulate pain." While this is correct, Applicant is claiming 'a method for detecting a pain-regulating substance' which means that ***any*** substance identified by the method must, by the definition of the preamble, regulate pain. Since there is no nexus between Vglut1 and pain, one skilled in the art could not use the invention to identify compounds as recited.

Therefore, for the reasons given in the office action of 6/14/05 and the reasons given above, it would require undue experimentation for one skilled in the art to make or use the invention as currently claimed.

6. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC § 112, 1st paragraph, enablement is maintained for the reasons made of record in the office action dated 6/14/05. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the amendment of claim 1 overcomes the rejection. The amendment to claim 1 includes a list of 'functional parameters' that includes measurement of regulation, inhibition, or activation of receptors, ion channels, or enzymes or via measurement of a modification in gene expression, ionic medium, pH or membrane potential, or via a modification in enzyme activity or concentration of second messenger.

However, neither the specification nor the art teach a relationship between Vglut1 and elements such as receptors, ion channels, enzymes, ionic medium, pH, enzyme activity or concentration of second messenger sufficiently for applicant to claim a generic 'measurement' of an enormous and varied genus of 'functional parameters' encompassed by the varied and unrelated things in the list above.

Applicant on page 11 of Remarks argues that at least in examples 5 and 6, procedures are provided in the specification sufficient to adequately show possession of the claimed invention. The examiner points out for the record that example 5 teaches making a fusion protein of Vglut1 for purification from bacteria, and then incubating said fusion protein in an in vitro assay with 32P-ATP and a substrate that is phosphorylated, such as a histone preparation from Sigma. The assay is putatively to be used to identify kinase inhibitors. The examiner further points out that ***no*** glutamate transporters polypeptides are known in the art as having kinase activity, and that the specification

does not demonstrate that Vglut1 has kinase activity, nor does ***anything*** teach measuring kinase activity in relation to a test molecule binding Vglut1.

Applicant on page 11 of Remarks argues that the claim "involves simply incubating a test substance with a biomolecule and then...measuring a functional parameter modified by this binding." Applicant further argues further on page 12 that "there is no requirement in the patent law that examples be provided," and that "a person of skill in the art would clearly understand that the applicants were in possession of the invention as defined by the claims." The examiner asserts once again that one skilled in the art could not envision an assay using the generic (and indefinite; see below) 'functional parameters' recited by the claims because neither the art nor the disclosure teach the relationship between Vglut1 and the functional parameters recited.

7. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC 112, 2nd paragraph for failing to adequately redefine the term ""a method of detecting a pain-regulating substance," is maintained for reasons made of record in the office action of 6/14/05.

8. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for being indefinite for reciting "stringent conditions" without first defining the meets and bounds of such conditions is maintained for reasons made of record in the office action of 6/14/05.

9. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for omitting essential steps is maintained for reasons made of record in the office action of 6/14/05.

10. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for being indefinite for because the relationship between the step a and step b is unclear is maintained for reasons made of record in the office action of 6/14/05.

11. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for using the term 'functional parameter,' without adequately defining it is maintained for reasons made of record in the office action of 6/14/05.

12. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for omitting a necessary ending step wherein a determination is made as to whether the compound is a pain regulating compound.

13. Rejection of Claims 4 under USC 112, 2nd paragraph for reciting expression of a form of G-protein without any clear relationship between it and the invention is maintained for reasons made of record in the action of 6/14/05.

14. Rejection of claims 2-4, and 7 under 35 USC § 112, 2nd paragraph, for 'genetic engineering' is maintained for reasons made of record in the office action of 6/14/05.

15. Claims 1-5, 7-12, and 14-15 are further rejected under 35 USC § 112, 2nd paragraph for reciting 'ionic medium.' It is not clear what the claim intends to measure when it recites 'ionic medium.' The specification gives no clear rendering of the definition, nor is it clear to one of skill in the art what "measurement of the regulation, inhibition or activation of ....ionic medium" means.

Claim Rejections - 35 USC § 102

Rejection of claims 1-3, 7-12, and 14 are under 35 USC § 102(e) over US application number 20020098473 is maintained for the reasons made of record in the

office action dated 6/14/05. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues on page 16 of remarks that the provisional of the application 20020098473 does not disclose a method for identifying compounds that modulate pain (wherein the limitation to pain is found in the preamble of the broad claim).

In response to applicant's arguments, the recitation "a method for detecting a pain-regulating substance..." has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Applicant also argues on page 16 of Remarks that the enzyme is not disclosed in the provisional. Applicant is directed to page 2 of the provisional 60/220,556 wherein 'BNPI' is disclosed as known in the art as Accession number AB032436 (one page alignment included as appendix a) which has 99.7% homology to that of SEQ ID NO: 4. Further, Applicant is claiming the method wherein 'BNPI' and variants with 90% homology are used. Furthermore, contacting BNPI with compounds and measuring (including the binding and transport of labeled glutamate and contacting with transport inhibitors) is disclosed in various places, including Figures 1-4 (pages 26-29).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven H. Standley whose telephone number is (571) 272-3432. The examiner can normally be reached on 8:00-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Janet Andre can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Steven Standley, Ph.D.

3/06/06

LORRAINE SPECTOR
PRIMARY EXAMINER

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: June 2, 2005, 11:19:52 ; Search time 178 Seconds
(without alignments)
1611.036 Million cell updates/sec

Title: US-10-734-731-4
Perfect score: 2970
Sequence: 1 MEFRQEEFRKLAGRALGKLH.....YGATHSTFQPPRPPPPVRDY 560

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1612378 seqs, 512079187 residues

Total number of hits satisfying chosen parameters: 1612378

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : UniProt_03:*
1: uniprot_sprot:*
2: uniprot_trembl:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	Query Match	Length	DB	ID	Description
1	2962	99.7	560	2	Q9P2U7	Q9p2u7 homo sapien
2	2953	99.4	560	2	Q6PCD0	Q6pcd0 homo sapien
3	2925	98.5	560	2	Q62634	Q62634 rattus norv
4	2460	82.8	576	2	Q6INC8	Q6inc8 xenopus lae
5	2444	82.3	576	2	Q715L3	Q715l3 xenopus lae
6	2338.5	78.7	584	2	Q8AW47	Q8aw47 brachydanio
7	2317.5	78.0	582	2	Q9P2U8	Q9p2u8 homo sapien
8	2313.5	77.9	582	2	Q920B7	Q920b7 mus musculu
9	2313.5	77.9	582	2	Q9JI12	Q9ji12 rattus norv
10	2308.5	77.7	582	2	Q8BLE7	Q8ble7 mus musculu
11	2198	74.0	588	2	Q8K1Q1	Q8k1q1 rattus norv
12	2198	74.0	588	2	Q7TSF2	Q7tsf2 rattus norv
13	2185	73.6	589	2	Q8NDX2	Q8ndx2 homo sapien
14	2154.5	72.5	601	2	Q8BFU8	Q8bfu8 mus musculu
15	2107	70.9	402	2	Q7TQH3	Q7tqh3 mus musculu
16	1981	66.7	515	2	Q8JFT2	Q8jft2 brachydanio
17	1358	45.7	592	2	Q7Q3R3	Q7q3r3 anopheles g
18	1297	43.7	576	1	YOQ6_CAEEL	P34644 caenorhabdi
19	1295.5	43.6	632	2	Q86P76	Q86p76 drosophila
20	1294	43.6	563	2	Q9TZN7	Q9tzn7 caenorhabdi
21	1198.5	40.4	560	2	Q9VQC0	Q9vqc0 drosophila
22	1051	35.4	201	2	Q8JZR7	Q8jzr7 mus musculu
23	1020	34.3	544	2	Q7Q580	Q7q580 anopheles g
24	986.5	33.2	502	2	Q9VDM0	Q9vdm0 drosophila
25	971	32.7	573	2	Q09932	Q09932 caenorhabdi
26	950	32.0	544	1	YRT3_CAEEL	Q10046 caenorhabdi
27	940	31.6	495	1	S175_HUMAN	Q9nra2 homo sapien
28	931	31.3	495	1	S175_SHEEP	Q9mzd1 ovis aries
29	931	31.3	476	2	Q7Q579	Q7q579 anopheles g
30	927	31.2	495	1	S175_MOUSE	Q8bn82 mus musculu
31	842	28.4	479	2	Q23514	Q23514 caenorhabdi
32	798	26.9	533	2	Q7Q1S5	Q7q1s5 anopheles g
33	798	26.9	559	2	Q9VYG7	Q9vyg7 drosophila
34	787	26.5	955	2	Q7Q367	Q7q367 anopheles g
35	775.5	26.1	493	1	YLD2_CAEEL	Q03567 caenorhabdi
36	774.5	26.1	535	2	Q7PWK4	Q7pwk4 anopheles g
37	767.5	25.8	529	1	PICO_DROME	Q9v7s5 drosophila
38	749	25.2	483	1	PICO_DROAN	O61369 drosophila
39	747	25.2	493	2	Q9VR44	Q9vr44 drosophila
40	743.5	25.0	541	2	Q8GX78	Q8gx78 arabidopsis
41	742.5	25.0	591	2	Q652N5	Q652n5 oryza sativ
42	727.5	24.5	485	2	Q7PSC6	Q7psc6 anopheles g
43	723.5	24.4	505	2	Q7QA73	Q7qa73 anopheles g
44	723.5	24.4	529	2	Q9SDI4	Q9sdi4 oryza sativ
45	720.5	24.3	512	2	O82390	O82390 arabidopsis

ALIGNMENTS

Appendix A

RESULT 1
Q9P2U7
ID Q9P2U7 PRELIMINARY; PRT; 560 AA.
AC Q9P2U7;
DT 01-OCT-2000 (TrEMBLrel. 15, Created)
DT 01-OCT-2000 (TrEMBLrel. 15, Last sequence update)
DT 01-OCT-2003 (TrEMBLrel. 25, Last annotation update)
DE Brain-specific Na-dependent inorganic phosphate cotransporter.
GN Name=BNPI;
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
RN [1]
RP SEQUENCE FROM N.A.
RC TISSUE=Brain;
RX MEDLINE=20281869; PubMed=10820226;
RA Aihara Y., Mashima H., Onda H., Hisano S., Kasuya H., Hori T.,
RA Yamada S., Tomura H., Yamada Y., Inoue I., Kojima I., Takeda J.;
RT "Molecular cloning of a novel brain-type Na(+)-dependent inorganic
RT phosphate cotransporter.";
RL J. Neurochem. 74:2622-2625(2000).
DR EMBL; AB032436; BAA92875.1; -.
DR Genew; HGNC:16704; SLC17A7.
DR GO; GO:0016021; C:integral to membrane; TAS.
DR GO; GO:0015321; F:sodium-dependent phosphate transporter acti. . .; TAS.
DR GO; GO:0006817; P:phosphate transport; TAS.
DR InterPro; IPR007114; MFS.
DR PROSITE; PS50850; MFS; 1.
SQ SEQUENCE 560 AA; 61613 MW; C88DAFB34B6B45B6 CRC64;

Query Match 99.7%; Score 2962; DB 2; Length 560;
Best Local Similarity 99.8%; Pred. No. 1.9e-214;
Matches 559; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

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Qy          1 MEFRQEEFRKLAGRALGKLHRLLEKRQEGAETLELSADGRPVTTQTRDPPVVDCTCFGLP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MEFRQEEFRKLAGRALGKLHRLLEKRQEGAETLELSADGRPVTTQTRDPPVVDCTCFGLP 60

Qy         61 RRYIIAIMSGLGFCISFGIRCNLGVAIVSMVNNSTTHRGGHVVVQKAQFSWDPETVGLIH 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 RRYIIAIMSGLGFCISFGIRCNLGVAIVSMVNNSTTHRGGHVVVQKAQFSWDPETVGLIH 120

Qy        121 GSFFWGYIVTQIPGGFICQKFAANRVFGPAIVATSTLNMLIPSAARVHYGCVIFVRILQG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GSFFWGYIVTQIPGGFICQKFAANRVFGPAIVATSTLNMLIPSAARVHYGCVIFVRILQG 180

Qy        181 LVEGVTYPACHGIWSKWAPPLERSRLATTAFCGSYAGAVVAMPLAGVLVQYSGWSSVFYV 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 LVEGVTYPACHGIWSKWAPPLERSRLATTAFCGSYAGAVVAMPLAGVLVQYSGWSSVFYV 240

Qy        241 YGSPGIFWYLFWLLVSYESPALHPSISEEERKYIEDAIGESAKLMNPLTKFSTPWRRFFT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 YGSFGIFWYLFWLLVSYESPALHPSISEEERKYIEDAIGESAKLMNPLTKFSTPWRRFFT 300
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